UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/814,873	12/24/91	WAYNER E	CYTE-1-6162

18M2/1014

CHRISTENSEN, O'CONNOR
JOHNSON & KINDNESS
2800 PACIFIC FIRST CENTRE
1420 FIFTH AVE.
SEATTLE, WA 98101

GAMBEL, EXAMINER	
ART UNIT	PAPER NUMBER
1806	27

DATE MAILED: 10/14/94

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☑ THE PERIOD FOR RESPONSE:

a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☑ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☑ Applicant's response to the final rejection, filed 9/19/94 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☑ Upon the filing an appeal, the proposed amendment ☑ will be entered ☐ will not be entered and the status of the claims will be as follows:

   Claims allowed: _____
   Claims objected to: 1-5, 32, 34-36
   Claims rejected: 1-5, 32, 34-36

   However;

   ☑ Applicant's response has overcome the following rejection(s): 112 1ST/2ND DUE TO APPLICANT'S AMD FROM "REGION" TO "FRAGMENT" (1-5, 32, 34-36)

4. ☑ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because _____
   — SEE ATTACHED —

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☑ Other . IDS HAS BEEN CONSIDERED
ATTACHED ① IDS
② 892 PLUS REF.
③ EXAM. RESPONSE

PTOL-303 (REV. 5-89)

4. The request for reconsideration has been considered but does not overcome the rejection because of the following:

Claims 1-5, 32 and 34-36 stand rejected under 35 U.S.C. § 101 and § 112, first paragraph, because the invention as disclosed is inoperative and therefore lacks utility and operability. The specification fails to establish the utility of the claimed $\alpha 4\beta 1$-specific antibodies as therapeutic agents to block lymphocyte adherence and migration in human patients.

Applicant argues that the examiner's references did not establish a prima facie case on non-utility and inoperability of the claimed invention. Applicant argues that their submitted in vivo data confirm the utility of the invention as disclosed in the application and the in vitro data set forth therein. Applicant again argues that the in vitro data would be predictive of antibody activity in vivo. Applicant reads the examiner's cited references of Harris et al. (Tibtech, 1993) and Waldmann (Science, 1991) as supporting the utility of antibody therapy rather than its lack of utility. Applicant argues that the FDA's approval does not indicate the lack of utility. Although applicant believes that no further support is necessary, applicant provides the use of the an $\alpha 4\beta 1$-specific antibody in a murine EAE model for multiple sclerosis.

The following is provided to rebut applicant's assertions that the examiner has not provided a prima facie case for the lack of utility and operability of the claimed invention and applicant's characterization of the art, including the examiner's cited references, to support predictability of antibody therapy without undue experimentation.

The examiner maintains that in vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunotherapeutic drugs can be species- and model-dependent, it is not clear that reliance on in vitro inhibition of binding by human cell lines or in vivo inhibition of an experimental animal model accurately reflects the relative efficacy of the claimed therapeutic strategy.

The examiner agrees that it is apparent that immunotherapy can be effective when applied to a highly defined model of inflammatory disease such as autoimmunity. However it is unclear whether this approach is feasible in the prevention or treatment of spontaneous autoimmune disease such as multiple sclerosis, diabetes or arthritis, in which the target autoantigens are not known and a number of autoantigens appear to be involved in the disease process. Furthermore, it is unclear whether such immunotherapy can be used to treat an ongoing autoimmune response

(which is the usual case) or whether it is effective only in terms of prevention. Generally, such diseases are diagnosed only after significant tissue damage has occurred. With respect to applicant's reliance the effects of $\alpha 4\beta 1$-specific antibody in a murine EAE model for multiple sclerosis (Yednock et al., Nature, 1992), multiple sclerosis is one of the most difficult disease in which to judge the effect of therapy since its natural history is unpredictable (Ebers, Lancet, 1994, particularly the first paragraph). Ebers further support the examiner's position above by stating that experimentally suppressing the secondary immune response anticipated in human autoimmune disease is much more difficult than suppressing the primary response to which therapy is directed in a transplant setting (e.g. experimental setting, see page 275, column 2, paragraph 2). Similarly, applicant's arguments that the claimed invention in the suppression of the immune and autoimmune responses in a wide range of diseases appears contrary to art-known limitations of animal models. For example, Brennan reviews those studies performed in animal models of arthritis which have investigated the role of cytokines in contributing to the pathogenesis of arthritis (Clin. Exp. Immunol., 1994). Although the animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses much more slowly over many years, with natural periods of disease exacerbation and remission. Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Curr. Opin. Immunol., 1992; see entire document, particularly page 558, column 2). Again, applicant's assertions on the predictability of in vitro assays and animal models does not appear to be consistent with art-known experience. Human diseases comprise multiple immune responses that makes therapeutic intervention a major hurdle even for known diseases.

Clearly, Harris et al. state that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3) (Tibtech, 1993). It is noted that this conference is the major annual meeting in the field of therapeutic monoclonals (page 44, column 1). The examiner maintains his reading of this clear statement rather than applicant's assertion. Waldmann clearly states that despite the wide ranging interest in monoclonal antibody therapy, the magic bullet of antibody therapy that has been the dream of immunotherapists since the time of

Paul Ehrlich has proved to be elusive (page 1657, paragraph 3). Only one monoclonal antibody, OKT3, has been licensed for clinical use. Applicant's concerns over the examiner's comments on the FDA are misplaced, as it was provided in this context as set forth by Waldmann. Furthermore, Jolliffe discloses that while OKT3 is effective for renal allograft rejection, OKT3 therapy for autoimmune diseases such as diabetes, multiple sclerosis and systemic lupus erythematosus has not been possible (Intern. Rev. Immunol., 1993).

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4).

Therefore, applicant's assertions that one of skill in the art would be able to treat immune diseases with predictability and without undue experimentation is not believable in view of art. Applicant has not provided sufficient evidence or nexus a priori that establishes the efficacy of the instant treatment of human disease with $\alpha 4\beta 1$-specific antibodies that is commensurate with the claimed invention. Therefore, it does not appear that the asserted utility and operability of the claimed method for treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

PG
Phillip Gambel, Ph.D.
October 11, 1994

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
10/13/94